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EXAMINER	
LOCKARD, JON MCCLELLAND	
ART UNIT	**PAPER NUMBER**
1647	

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12/08/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,004	WALCZAK, HENNING	
	Examiner	Art Unit	
	JON M. LOCKARD	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 July 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-51* is/are pending in the application.

4a) Of the above claim(s) *6-8,27-32,39 and 45-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,9-26,33-38 and 40-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-51* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 September 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/14/07, 9/19/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 1-5, 9-26, 33-38, and 40-44, in so far as they are drawn to CD95/Ig fusion proteins and nucleic acids encoding the same, in the reply filed on 08 March 2010 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 6-8, 27-32, 39, and 45-51 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 08 March 2010.

2. The restriction requirement is still deemed proper and is therefore made FINAL.

Status of Application, Amendments, and/or Claims

3. The response filed 08 March 2010 has been received and entered in full. Claims 29 and 32 have been amended, and 6-8, 27-32, 39, and 45-51 have been withdrawn. Therefore, claims 1-5, 9-26, 33-38, and 40-44, in so far as they are drawn to CD95/Ig fusion proteins and nucleic acids encoding the same, are the subject of this Office action.

Information Disclosure Statement

4. The information disclosure statements (IDS) submitted on 14 August 2007 and 19 September 2007 have been considered by the examiner.

Specification

5. The disclosure is objected to because of the following informalities: The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Appropriate correction is required.

Claim Objections

6. Claims 2, 4, and 5 are objected to because of the following informalities: they encompass non-elected inventions, i.e., receptor-binding domain of a ligand (claim 2), growth factor receptors and cytokine receptors (claim 4), and TRAIL receptor, TNF receptor, and VEGF receptor (claim 5). Appropriate correction is required.

7. Claim 26 is objected to because of the following informalities: it fails to comply with 37 C.F.R. § 1.821(d) which requires a reference to a particular sequence identifier (i.e., SEQ ID NO:#) be made in the Specification and claims whenever a reference is made to that sequence. See also MPEP 2422.04. Appropriate correction is required.

8. Although not indefinite, it is suggested for the purpose of clarity that the limitation "located on" in claim 35, be amended to "comprised in", which is more consistent with the language utilized in the art.

Claim Rejections - 35 USC § 112, 2nd Paragraph

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-5, 9-26, and 33-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. Claims 1, 16, 17, 23, and 44 are rejected as being indefinite because it is unclear what is meant by an overlap between the amino acid sequences. Does it refer to immunogenic activity, IL-10 receptor-mediated activity, or some other activity? Since neither the specification nor the art provide an unambiguous definition of the term, the metes and bounds of the claim cannot be determined.

12. Claim 33 is rejected as being indefinite for reciting the phrase, "or a precursor thereof". Since it is unclear what a precursor of a fusion protein would be, the metes and bounds of the claim cannot be determined.

13. Claims 9 and 15 are rejected as being indefinite for reciting the term, "derived from". Does it refer to a protein obtained from a human source, or does it refer to a protein that has been altered (i.e., via deletions, additions, and/or substitutions) in comparison to a reference human protein? Since it is unclear, the metes and bounds of the claims cannot be determined.

14. Claim 44 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The preamble recites "A method for manufacturing a fusion protein", but the claim does not recite any active method steps.

15. Claims 2-5, 10-14, 18-22, 24-26, and 33-43 are rejected for depending from an indefinite claim.

Claim Rejections - 35 USC § 112, 1st Paragraph (Scope of Enablement)

16. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

17. Claims 1-5, 9-26, 33-38, and 40-44 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a fusion protein comprising the amino acid sequence SEQ ID NO:15 and a nucleic acid molecule encoding the same, as well as compositions comprising the fusion protein or nucleic acid molecule and a pharmaceutically acceptable carrier, does not reasonably provide enablement for (1) a fusion protein comprising at least one first domain comprising *any* biologically active polypeptide fused to a heterologous second protein comprising at least *a portion* of a constant immunoglobulin domain, and nucleic acid molecules encoding the same; (2) a fusion protein comprising an amino acid sequence as shown in Figures 3A and 3B (it is noted that the recitation of "an amino acid sequence" can be interpreted to mean a partial sequence, as few as two amino acid residues); (3) a nucleic acid encoding a precursor of a fusion protein comprising at least one first domain comprising *any* biologically active polypeptide fused to a heterologous second protein comprising at least *a portion* of a constant immunoglobulin domain; (4) non-isolated cells comprising a nucleic acid encoding a fusion protein comprising at least one first domain comprising *any* biologically active polypeptide fused to a heterologous second protein comprising at least *a portion* of a constant immunoglobulin domain; and (5) pharmaceutical compositions comprising a nucleic acid encoding a fusion protein comprising at least one first domain comprising *any* biologically active

polypeptide fused to a heterologous second protein comprising at least *a portion* of a constant immunoglobulin domain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

18. The specification's disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation. The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

19. The claims are drawn quite broadly to (1) a fusion protein comprising at least one first domain comprising *any* biologically active polypeptide fused to a heterologous second protein comprising at least *a portion* of a constant immunoglobulin domain, and nucleic acid molecules encoding the same; (2) a fusion protein comprising an amino acid sequence as shown in Figures 3A and 3B (it is noted that the recitation of "an amino acid sequence" can be interpreted to mean a partial sequence, as few as two amino acid residues); and (3) a nucleic acid encoding a precursor of a fusion protein comprising at least one first domain comprising *any* biologically active polypeptide fused to a heterologous second protein comprising at least *a portion* of a constant immunoglobulin domain. While the Specification discloses a CD95-Fc fusion protein

comprising the amino acid sequence SEQ ID NO:15 which promotes regeneration and functional recovery after spinal cord injury (See pg. 17), it does not teach a commensurate number of the claimed polypeptides or nucleic acid molecules encoding them. Other than the polypeptide of SEQ ID NO:15, the disclosure fails to provide sufficient guidance and information regarding the structural and functional requirements commensurate in scope with what is encompassed by the instant claims. The disclosure has not shown (1) which portions of the protein of SEQ ID NO:15 are critical to the activity of the protein of SEQ ID NO:15; (2) what modifications e.g., substitutions, deletions, or additions) one can make to SEQ ID NO:15 that will result in protein mutants or variants with the same function/activity as the protein of SEQ ID NO:15; and (3) any guidance on how to use the variants of SEQ ID NO:15 which would, based on the language of said claims, encompass both active and inactive variants, especially in the absence of any structural or functional limitations in the claims. The state of the art is such that the relationship between the sequence of a protein and its activity is not well understood and unpredictable, and that certain positions in the sequence are critical to the protein's structure/function relationship and can only tolerate only relatively conservative substitutions or no substitutions.

20. The problem of predicting protein and DNA structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and DNA is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-

dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions and still retain the activity of the protein of SEQ ID NO:15.

21. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

22. Furthermore, it is noted that the Examiner has interpreted claim 36 as reading on a cell in the context of (1) isolated host cells in culture to produce the encoded protein recombinantly, (2) genetically engineered host cells to express such products in vivo for use in gene therapy, and (3) expression in transgenic animals. However, there are no methods or working examples disclosed in the instant application that indicate the claimed nucleic acid is introduced and expressed in a

cell or organism for therapeutic purposes. The specification does not teach what type of vector would introduce the claimed nucleic acid into the cell or the subject, or in what quantity and duration. Gene therapy is unpredictable and complex wherein one skilled in the art may not necessarily be able to introduce and express the claimed nucleic acid in the cell of an organism or be able to produce the encoded protein in that cell. Relevant literature teaches that since 1990, about 3500 patients have been treated via gene therapy and although some evidence of gene transfer has been seen, it has generally been inadequate for a meaningful clinical response (Phillips, A.J., J. Pharm. Pharmacol. 53: 1169-1174, 2001; see abstract; See also Palù et al. J. Biotechnol. 68:1-13, 1999). Additionally, the major challenge to gene therapy is to deliver DNA to the target tissues and to transport it to the cell nucleus to enable the required protein to be expressed (Phillips, A.J.; pg 1170, ¶ 1). Phillips also states that the problem with gene therapy is two-fold: 1) a system must designed to deliver DNA to a specific target and to prevent degradation within the body, and 2) an expression system must be built into the DNA construct to allow the target cell to express the protein at therapeutic levels for the desired length of time (pg 1170, ¶ 1). Therefore, undue experimentation would be required of the skilled artisan to introduce and express the claimed nucleic acid into the cell of an organism to treat disease.

23. Furthermore, there are no methods or working examples disclosed in the instant application whereby a multicellular animal with the incorporated gene is demonstrated to express the encoded claimed polypeptide. The unpredictability of the art is very high with regard to making transgenic organisms. For example, Wang et al. (Nuc. Acids Res. 27:4609-4618, 1999) surveyed gene expression in transgenic animals and found each experimental animal with a single "knock-in" gene, multiple changes in genes and protein products, often many of which

were unrelated to the original gene (See pg 4617). Likewise, Kaufman et al. (Blood 94:3178-3184, 1999) found transgene expression levels in their transfected animals varied from "full" (9%) to "intermediate" to "none", due to factors such as vector poisoning and spontaneous structural rearrangements (See pg 3180, col. 1; pg 3182-3183).

24. Due to the large quantity of experimentation necessary to generate a transgenic animal expressing the disclosed fusion protein and to introduce the claimed nucleic acid in the cell of an organisms for therapy; the lack of direction/guidance presented in the specification regarding how to introduce the claimed nucleic acid into the cell of an organism to be able to produce the encoded protein, the absence of working examples directed to the same; the complex nature of the invention; the state of the prior art which establishes the unpredictability of making transgenic animals and the unpredictability of transferring genes into an organisms cells; undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

25. Please note that this issue could be overcome by amending claim 36 to recite, for example, "An isolated host cell", and amending claim 40 to recite, for example, "A composition comprising the fusion protein of claim 1, or a nucleic acid molecule of claim 33, and a pharmaceutically acceptable carrier".

Summary

26. No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jon M. Lockard, Ph.D.** whose telephone number is **(571) 272-2717**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Nickol, Ph.D.**, can be reached on **(571) 272-0835**. The fax number for the organization where this application or proceeding is assigned is **571-273-8300**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see **http://pair-direct.uspto.gov**. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jon M. Lockard, Ph.D.
December 6, 2010

/Jon M Lockard/
Examiner, Art Unit 1647